Changes in Left and Right Ventricular Mechanics During the Mueller Maneuver in Healthy Adults

A Possible Mechanism for Abnormal Cardiac Function in Patients With Obstructive Sleep Apnea

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Background—Obstructive sleep apnea is highly prevalent in patients with cardiovascular disease and has detrimental effects on systolic and diastolic function of the ventricles. In this research, the changes in strain (S) and strain rate (SR) during the performance of the Mueller maneuver (MM) in an effort to better understand how negative intrathoracic pressures affect ventricular mechanics.

Methods and Results—The MM was performed to maintain a target intrathoracic pressure of −40 mm Hg. Echocardiography was used to measure various parameters of cardiac structure and function. Myocardial deformation measurements were performed using tissue speckle tracking. Twenty-four healthy subjects (9 women; mean age, 30±6 years) were studied. Global left ventricular longitudinal S in systole and SR in early filling were significantly decreased during the MM (S: baseline, −17.0±1.6%; MM, −14.5±2.2%; P<0.0001, SR: baseline, 1.09±0.20 s⁻¹; MM, 0.92±0.21 s⁻¹; P=0.01). Global right ventricular longitudinal S was also significantly decreased during the MM (baseline, −22.0±3.1%; MM, −17.2±2.5%; P<0.0001), as was global right ventricular longitudinal systolic SR (baseline, −1.34±0.35 s⁻¹; MM, −1.02±0.21 s⁻¹; P=0.0006).

Conclusions—Left ventricular and right ventricular longitudinal deformation are significantly reduced during the MM. These results suggest that negative intrathoracic pressure during apnea may contribute to changes in myocardial mechanics. These results could help explain the observed changes in left ventricular and right ventricular mechanics in patients with obstructive sleep apnea. (Circ Cardiovasc Imaging. 2010;3:282-289.)

Key Words: obstructive sleep apnea • ventricles • echocardiography • strain

Obstructive sleep apnea (OSA) is characterized by repetitive apneic events, intermittent hypoxia, and arousals occurring during sleep. The prevalence of OSA is as high as 20% in the adult population.¹⁻⁵ Apneic events are caused by collapse of the pharyngeal airway associated with vigorous ventilatory efforts that lead to generation of high negative intrathoracic pressure.⁶

Chronic OSA has been associated with a variety of cardiovascular complications.⁷ These include sudden cardiac death,⁸ heart failure,⁹ hypertension,¹⁰ acute myocardial infarction,¹¹ and arrhythmias.¹²,¹³ Such findings suggest that OSA may directly affect myocardial performance and cardiovascular outcomes. However, it is not certain that OSA is an independent risk factor for left ventricular (LV) and right ventricular (RV) dysfunction. Potential mechanisms by which OSA might adversely impact LV function include abrupt increases in afterload resulting from high negative intrathoracic pressure at the onset of an obstructive apnea and the subsequent increase in sympathetic nerve activity and blood pressure.¹⁴ The apneic events in OSA, lasting 10 seconds or more, are also associated with hypoxia and hypercapnia, which may impair cardiac contractility directly or, in the case of the right ventricle, indirectly, by increasing pulmonary artery pressure.

In recent years strain (S) and strain rate (SR) imaging by 2D speckle tracking have been used to quantify myocardial deformation, and the rate of deformation, in both the LV and the RV.¹⁵ These new techniques might better characterize...
cardiac abnormalities associated with OSA than standard Doppler echocardiography.

**Methods**

Twenty-four healthy young adults with normal body mass index and normal sinus rhythm participated in this study. The protocol was reviewed and approved by Mayo Clinic Institutional Review Board. Data from a subgroup of these participants were published earlier.16

**Study Protocol**

Baseline measurements were recorded during quiet breathing and at the end of expiration while in the supine position before each Mueller maneuver (MM). Subjects wore a nose clip and a mouthpiece with a small air leak through a 21-gauge needle to prevent closure of the glottis during the MM. Mouth pressure was visually monitored by each subject to maintain the target intrathoracic pressure of \(40\) mm Hg. All subjects performed several practice MMs before data collection started. Subjects performed 10 MMs, each lasting 12 seconds, separated by a 3-minute rest period. Echocardiography loops, ECG, and bioimpedance curves were recorded at baseline, during the MM and 10 minutes after termination of the last MM (recovery). Blood pressure was taken by cuff at the time of echocardiography and monitored throughout the whole study using a continuous blood pressure monitoring system (TDP Biomedical Instrumentation, Amsterdam, The Netherlands).

**Image Acquisition**

Complete 2D and Doppler echocardiographic imaging was performed according to the standards of the American Society of Echocardiography. All echocardiographic data were stored on the hard drive of the echocardiographic machine (Siemens Sequoia C512, Mountain View, Calif) and copied to compact discs for further off-line analysis. Measurements were performed at baseline, during the MM, and 10 minutes after the last MM (recovery). The average frame rate for the acquired images was 36 MHz. Images were acquired from the peak of the R wave, and at least 1 complete cardiac cycle was used for analysis. Apical 4-chamber (A4C) and apical 3-chamber (A3C) views were analyzed in each patient. The images were downloaded from the central archive and stored in DICOM format either on magneto-optical disks or on a computer hard drive. The images were then imported for analysis to a velocity vector imaging (VVI) program (Syngo VVI version 2.0 software program; Siemens Healthcare, Malvern, Pa).

**Image Analysis**

Three-beat cine-loop clips were selected from the A4C and A3C views at baseline, during the MM, and after recovery. For the MM, we analyzed 3 stored cine clips after 8 seconds of its initiation. For each patient, 12 segments were analyzed for the LV and 6 segments for the RV. Ten to 15 points were placed in the myocardium starting and ending at the mitral or tricuspid annulus. The tracing was performed at end-systolic or midsystolic frame, whichever had better endocardial definition. The quality of the tracking was assessed visually and the process was repeated, as needed, to ensure satisfactory tracking of the myocardium.

**Strain and Strain Rate Analysis**

We used VVI for the measurement of myocardial S and SR from 2D images. This offline software provides angle-independent measurement of 2D velocity, displacement, S, and SR. It is a quantitative method that provides regional and global myocardial mechanics, through the combination of speckle tracking, tissue-blood border detection, the periodicity of the cardiac cycle using R-R intervals,
and generation of M-mode representations of the segments with mitral annulus motion.

Once a satisfactory trace was obtained, the images were processed by the software to obtain longitudinal velocity, S, SR, and displacement, as well as the time to peak (TTP) for each segment, (12 segments of the LV [A4C and A3C views], and 6 segments of the RV [A4C view]). The velocity, S, systolic SR (SRs), SR in early filling (SRe), and displacement of each segment were calculated by the software as an average of a number of points of interest within the region. Global LV and RV values were calculated by averaging the value of 6 segments in the A4C for the RV and 12 segments in the A4C and A3C for the LV. Average S and SRs of the basal, mid, and apical regions were also calculated. Figure 1 and Figure 2 show examples of S and SR curves at baseline, during the MM, and recovery phases of the LV and RV, respectively.

Reproducibility
Interobserver variability was assessed with speckle-tracking echocardiography in 8 randomly selected patients for 3 predetermined beats of images during baseline and the MM; these were independently performed by 2 investigators. Intraobserver reproducibility was assessed by repeating the speckle-tracking echocardiography examinations in 3 predetermined beats of images during baseline in 8 randomly selected patients for masked review by the same investigator 4 to 8 weeks after the initial analysis. Intraobserver and interobserver variability were assessed for S and SR, as well as TTP for each of these variables.

Statistical Analysis
Data are presented as mean±SD. One-way repeated-measures ANOVA was used to determine significant differences among the individual segments for S, SR, velocity, and displacement and the TTP among 3 phases. To assess difference each of these variables between baseline and the MM and between the MM and recovery, was used paired t test. In figure, the box plots summarize the distribution of points at each factor level and the 25th and 75th quartiles. For intraobserver and interobserver variability, we calculated the Bland-Altman 95% limits of agreement. We calculated the mean absolute difference between the 2 observers and the percentage of the difference relative to the sample mean value for each variable. The percentage difference was calculated as the absolute difference of the 2 sets of measurements divided by the mean of the measurements. The limits of agreement were calculated as standard deviations of the absolute difference between the 2 observers. A probability value of <0.05 was considered statistically significant. JMP Statistical Discovery version 7 software (SAS Institute, Cary, NC) was used to perform the statistical analysis.

Results
Demographics
The baseline characteristics and echocardiographic data of the 24 subjects are shown in Table 1. The mean age was 30±6 years, 63% were men, and mean body mass index was 23.7±2.7 kg/m². The mean LV ejection fraction (LVEF) was 64±4% without any abnormal findings at baseline. As we reported in a previous article including a part of this study population, LVEF, stroke volume, cardiac output, and cardiac index were decreased significantly (P<0.0001) during the MM, whereas LV systolic dimension and septal E/E′ ratio were increased (Table 2).

LV Longitudinal Strain and Strain Rate
The means (±SD) of the S, SRe, and SRe for the basal, mid, and apical segments of the LV and RV along with the TTP of
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>24</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Age, y</td>
<td>30±6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.7±2.7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64±10</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122±16</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>69±10</td>
</tr>
<tr>
<td>Frame rate, Hz</td>
<td>35.6±2.9</td>
</tr>
</tbody>
</table>

Average global RV longitudinal strain overall was not significantly different from baseline. Each of these variables in the longitudinal view are shown in Table 3. In terms of global myocardial function, the average LV longitudinal S at baseline was −17.0±1.6% and the average TTP was 382±28 ms. During the MM, global S was reduced to −14.5±2.2% (P<0.0001); after termination of the MM, S increased to −16.3±2.4% in the recovery phase (P<0.0001) (Figure 3). Significant changes were also noted for the base, mid, and apex of the LV segments (Table 3). The average global longitudinal SRs at baseline was −0.95±0.13 s⁻¹ and the overall average TTP of SRs at baseline was 190±32 ms. Although there was a significant difference between the MM (−0.87±0.12 s⁻¹) and baseline (P=0.02), there was no significant difference between the MM and recovery (−0.87±0.12 s⁻¹) in global SRs. The average global longitudinal SRs and TTP at baseline were 1.09±0.20 s⁻¹ and 488±38 ms. During the MM, global SRs was reduced to −0.92±0.21 s⁻¹ (P=0.01); after termination of the MM, SRs increased to 1.03±0.27 s⁻¹ in the recovery phase (P=0.03) (Figure 4). TTP did not vary between baseline, the MM, and recovery. Although S and SR did change between the different phases, dyssynchrony was not present.

Table 2. Echocardiographic Features (n=24)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Mueller Maneuver</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic dimension, mm</td>
<td>47±4</td>
<td>47±5</td>
<td>0.3</td>
</tr>
<tr>
<td>LV systolic dimension, mm</td>
<td>30±3</td>
<td>32±3</td>
<td>0.0004</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>64±4</td>
<td>56±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>77±15</td>
<td>56±16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>48±0.9</td>
<td>3.7±1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac index, L/min/mm²</td>
<td>2.6±0.4</td>
<td>1.9±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>1.8±0.3</td>
<td>1.9±0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Deceleration time of E velocity, ms</td>
<td>213±34</td>
<td>205±33</td>
<td>0.3</td>
</tr>
<tr>
<td>Septal E/E’ ratio</td>
<td>4.8±1.2</td>
<td>5.8±1.3</td>
<td>0.003</td>
</tr>
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</table>

RV Longitudinal Strain and Strain Rate

Average global RV longitudinal strain overall was −22.0±3.1%, with an average global TTP of 403±36 ms. Global RV S decreased to −17.2±2.5% during the MM (P<0.0001) and returned to −21.3±3.2% during the recovery phase (P<0.0001 for both) (Figure 5). Significant changes were also noted for the base, mid and apex of the RV segments (Table 3). The average global longitudinal SRs in RV systole (SR), s⁻¹

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Mueller Maneuver</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>−0.97±0.13</td>
<td>−0.89±0.17‡</td>
<td>−0.89±0.21</td>
</tr>
<tr>
<td>Mid</td>
<td>−0.99±0.13</td>
<td>−0.93±0.18‡</td>
<td>−0.91±0.16</td>
</tr>
<tr>
<td>Apex</td>
<td>−0.89±0.25</td>
<td>−0.80±0.15</td>
<td>−0.82±0.22</td>
</tr>
<tr>
<td>Global</td>
<td>−0.95±0.13</td>
<td>−0.87±0.12‡</td>
<td>−0.87±0.17</td>
</tr>
<tr>
<td>Time to peak, ms</td>
<td>190±32</td>
<td>177±33</td>
<td>189±28</td>
</tr>
<tr>
<td>Strain rate in early RV filling (SRe), s⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>1.00±0.26</td>
<td>0.94±0.29</td>
<td>0.93±0.28</td>
</tr>
<tr>
<td>Mid</td>
<td>1.16±0.22</td>
<td>1.04±0.27</td>
<td>1.12±0.29</td>
</tr>
<tr>
<td>Apex</td>
<td>1.09±0.26</td>
<td>0.78±0.23‡</td>
<td>1.04±0.36</td>
</tr>
<tr>
<td>Global</td>
<td>1.09±0.20</td>
<td>0.92±0.21‡</td>
<td>1.03±0.27</td>
</tr>
<tr>
<td>Time to peak, ms</td>
<td>488±38</td>
<td>464±50</td>
<td>492±38</td>
</tr>
</tbody>
</table>

RV at baseline was −1.34±0.35 s⁻¹ and the overall average TTP was 225±34 ms. SRs decreased during the MM (−1.02±0.21 s⁻¹, P=0.0006) and improved during recovery (−1.23±0.29 s⁻¹, P=0.005) (Figure 6). Significant decreases in SRs were seen in the basal and mid segments of RV.
the RV during the MM (basal, $-1.15\pm0.30$ s$^{-1}$; mid, $-1.06\pm0.31$ s$^{-1}$) compared with baseline (basal, $-1.58\pm0.51$ s$^{-1}$, $P=0.002$; mid, $-1.41\pm0.41$ s$^{-1}$, $P=0.004$) (Table 3).

Reproducibility
Tracking accuracy of speckle-tracking echocardiography was assessed visually. The intraobserver and interobserver variability as measured by mean absolute differences for S and SRs in the LV were minimal and relatively small, compared with the actual strain scale of all the readings in both LV and RV. Details are provided in Table 4.

Discussion
In this study, we evaluated changes in longitudinal LV and RV deformation during the MM in healthy volunteers. Global LV and RV strain were significantly reduced, returning to baseline values during the recovery phase. Global RV strain rate in systole and global LV strain rate during early filling were also significantly reduced during the MM.

Changes in Cardiac Function During the MM
To the best of our knowledge, this is the first report investigating the effect of the MM on ventricular S and SR. Our study provides new information to better understand the association between LV and RV dysfunction in patients with OSA.$^{17,18}$ Previous work confirmed that the MM closely simulated changes in intrathoracic pressure produced during sleep in subjects with OSA and increases sympathetic nervous activity.$^{19,20}$ Acute increase in right-heart volume should be induced by the fall in pleural pressure with the MM.$^{21,22}$ Additionally, there is simultaneous increase in transmural right ventricular filling pressure and decrease in RV ejection fraction.$^{23}$ In the left heart, the abrupt negative intrathoracic
pressure imposes an afterload burden on the LV and a fall in cardiac output and stroke volume. To the extent that LV compliance is decreased, the LV end-diastolic pressure will tend to rise. Our previous work showed a significant decrease in LVEF during the MM. In the present study, further changes in cardiac function were evidenced with altered S and SR during the MM not only in the LV but also in the RV. Our results suggest that abrupt negative intrathoracic pressure deteriorated RV mechanical function because of increases in pulmonary artery transmural pressure and RV afterload during the MM.

**Left and Right Ventricular Dysfunction Related to OSA**

In a large cross-sectional study, Chami et al reported greater LV mass index, larger LV diastolic dimension, and lower LVEF were associated with a higher apnea-hypopnea index (AHI) and higher hypoxemia index. On the other hand, Nimoumand et al reported that OSA was not associated with increased LV mass or impaired LV diastolic function. Little is known about mechanisms by which OSA might lead to cardiac dysfunction. Both LV and RV systolic impairment can occur in patients with significant OSA. However, patients with OSA often have coexisting disorders that might also produce ventricular dysfunction, such as obesity, aging, hypertension, and coronary artery disease. It is unclear if the negative intrathoracic pressure in OSA is predictive of impaired ventricular function independent of other conditions. In the present study, however, we were able to demonstrate adverse effects of negative intrathoracic pressure on both RV and LV mechanical function in young adults without comorbidities. These findings would shed a new light on better understanding the mechanisms of deterioration in cardiac function due to negative intrathoracic pressure as one of the most characteristic pathophysiologic changes in OSA.

**Two-Dimensional Speckle Tracking Analysis of Cardiac Function**

Changes in S and SR as assessed by 2D speckle tracking may provide a useful tool for the characterization and early evaluation of cardiac dysfunction. S and SR measurements offer advantages over regional myocardial velocities, which can be affected by tethering from other myocardial segments and translational motion of the entire heart. Dokainish et al reported systolic S and SRs were significantly depressed in patients with preserved LVEF of 59±5% but elevated LV end-diastolic pressure (>20 mm Hg) using invasive hemodynamics. Lopez-Candales et al reported peak longitudinal strain in the RV was a significant predictor of RV performance in patients with pulmonary hypertension. In the present study, our findings of changes in S and SR indicate that RV and LV function were impaired during the MM. This suggests that sudden changes in loading conditions cause transient LV and RV dysfunction. Repetitive obstructive apneas over time, such as those that occur in OSA, might therefore be expected to have cumulative deleterious effects on both the right and left ventricles.

**Limitations**

It is possible that some of the comparisons that did not show any significant change in regional or total S or SR could be due to small sample size. Patients with poor echocardiographic windows can pose a challenge to the accurate measurement of S and SR by 2D echocardiography. Tracking can also be affected by patient movement during the MM as well as movement of the heart within the chest. In the present study, we measured longitudinal S and SR; radial S and SR are also measures of LV systolic function and would be of interest to pursue in future studies. Additionally, the MM only partially reproduced the pathophysiologic changes seen in OSA. Although altering intrathoracic pressure, intracardiac hemodynamics, and stimulating catecholamine release with the MM, the duration of the MM itself is short and may not replicate entirely the repetitive obstructive apneas in patients with OSA. The measurements were not blinded to the stage of the MM because of technical limitations that would make it nearly impossible to mask the MM stage, as the EKG tracing needed to perform the strain analysis is usually distorted during the MM.

**Conclusion**

Global S and SR in the LV and the RV were significantly decreased during the MM in healthy adults. These results indicate that the imposition of abrupt negative intrathoracic pressure can acutely impair ventricular mechanics. Our findings may provide useful insights into mechanisms of cardiac dysfunction in patients with OSA.

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Disclosures

Dr Somers has served as a Consultant for ResMed, Boston Scientific, Cardiac Concepts, and Sepacor and as an investigator on research grants funded by the Respiroscins Sleep and Breathing foundation, Sorin Inc and Select Research.

References


Although obstructive sleep apnea (OSA) has been implicated in the genesis of myocardial dysfunction, the mechanisms by which OSA affects myocardial function have not been determined. In this study, we focused on the effect of negative intrathoracic pressure, which is a characteristic pathophysiological change in OSA, on cardiac mechanics using 2D speckle tracking analysis. The Mueller maneuver was performed to simulate OSA in 24 healthy volunteers. During this procedure, a negative intrathoracic pressure of $-40$ mm Hg was maintained for 12 seconds. We measured longitudinal strain and strain rate at baseline, during the Mueller maneuver, and at recovery. Our principal findings were that during the Mueller maneuver, global longitudinal strain and strain rate in the left ventricle were significantly reduced compared with baseline. These results suggest that negative intrathoracic pressure during apnea may contribute to changes in myocardial mechanics. These findings provide one mechanism through which OSA may be linked to cardiac dysfunction.
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